Discussion Topics and Voting Question for the Advisory Committee

1. Risks

The most common adverse events associated with MCNA in Studies 301 and 303 were hematuria, dysuria, fatigue, UTI, pollakiuria, and micturition urgency. There were no deaths related to MCNA instillation.

Discussion Topic # 1a: *Please discuss the safety of MCNA for the intended patient population.*

Study 301 enrolled subjects with non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression who had failed prior Bacillus Calmette-Guérin (BCG) treatment. The main treatment option for these subjects is cystectomy. Delaying cystectomy might predispose these subjects to develop invasive and metastatic bladder cancer (MBC) and death. Fifteen (11.6%) subjects developed MBC in Study 301. However, follow-up information was limited for many subjects because of the early trial closure.

Discussion Topic # 1b: *Please discuss the safety concern that treatment with MCNA may delay cystectomy and thereby increase the incidence of MBC in the intended patient population.*

After MCNA treatment, frequent follow-up and vigilant surveillance to detect any persistent CIS-containing disease could lead to immediate cystectomy and thus mitigate the risk of developing invasive disease or metastatic bladder cancer.

Discussion Topic # 1c: *Please discuss and make suggestions for a monitoring plan to mitigate the potential risk of disease progression in patients who initiate MCNA treatment rather than proceeding to cystectomy.*

2. Benefits

Study 301 was a single-arm trial with the primary endpoint of disease-free survival at one year (DFS 1y). The patient population included 129 adult subjects with NMIBC at high risk of recurrence or progression who had failed prior BCG treatment. These subjects had different histologies at baseline: high-grade Ta and/or T1 papillary lesion(s), as well as carcinoma in situ (CIS) either alone or with papillary lesion(s) of any grade(s) (CIS-containing disease). The primary study objective was to show a true DFS 1y rate of at least 40%. The trial failed to meet this pre-specified threshold for success. However, in light of the limited treatment options for patients with BCG-refractory NMIBC, FDA views the trial results, especially the results in the subpopulation of subjects with CIS-containing disease, worth consideration in an advisory committee meeting.

FDA review of this BLA has identified the following issues regarding both the study design and the study results:

a. The inherent limitations of the single-arm trial design without a concurrent control;
b. The reliability of DFS assessments
c. The difficulty in reliably estimating the effect size of the primary endpoint of DFS 1y

Discussion Topic # 2:

Given the above background, please discuss the benefit of MCNA for the proposed indication "for the treatment of non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing."

3. Benefits in CIS-containing and Papillary-only Subgroups of Study 301

As discussed in Section 7.4 of FDA Briefing Document, in subjects with CIS-containing disease, MCNA treatment was associated with a 27% complete response (CR) at 6 months with an median duration of response (mDOR) of 15.1 months from the time when subjects first achieved CR (or 18.1 months from start of MCNA treatment) to the last evaluation that did not identify the recurrence of any bladder cancer. Although not pre-specified in the trial design, these results might provide evidence of effectiveness for MCNA. Since active CIS disease does not usually regress on its own, complete response in this setting would reflect a treatment effect from MCNA. In addition, some subjects had CR that lasted more than two years and did not require cystectomy.

Discussion Topic # 3a: *Please discuss the benefit of MCNA treatment in subjects with CIS-containing disease.*

The protocol of Study 301 mandated that subjects with papillary-only disease undergo transurethral resection of the bladder tumor (TURBT) prior to or within eight weeks of the 1st dose of MCNA treatment. Thus, these subjects were rendered disease-free at or soon after the onset of the study treatment. Because they had undergone surgical resection at the baseline, it is uncertain whether the disease-free status at one year reflected a treatment effect from MCNA or a result of the surgical resection. Disease-free survival for subjects who have no disease at baseline is usually difficult to evaluate in the context of a single-arm trial without concurrent control.

Discussion Topic # 3b: *Please discuss the benefit of MCNA treatment in subjects with papillary-only disease.*

4. Proposed Indication

The enrolled subjects in Study 301 had failed prior BCG therapy according to the protocol-defined criteria. However, the Applicant added "BCG-relapsing" for analysis after the termination of Study 301 to denote 22 (17%) subjects who were disease-free at Month 6 following the start of BCG induction, as opposed to "BCG-refractory" subjects [107 (83%)] who were not disease-free at Month 6 following the start of BCG induction. The median number of prior BCG instillations was 15 (range 9-32) in the BCG-relapsing group, and 12

(range 5-33) in the BCG-refractory group. BCG-relapsing subjects had a numerically higher DFS 1y compared with BCG-refractory subjects (36% vs. 19%).

Discussion Topic # 4a: *Please discuss whether the biology and prognosis of BCG-relapsing disease differ from those of BCG-refractory disease.*

Discussion Topic # 4b: *Please discuss whether there are any issues/concerns regarding the proposed patient population: adult patients with NMIBC at high risk of recurrence or progression who failed prior Bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing.*

5. Prior Treatment with BCG

While the precise immunological mechanism(s) of action (MOA) of MCNA is unknown, it is likely to share many commonalities with BCG-mediated immunostimulation. However, differences between MCNA (a sterile aqueous suspension containing *M. phlei* cell wall fragments complexed with nucleic acid oligomers) and BCG (a suspension of live, attenuated Bacillus Calmette-Guérin, derived from *M. bovis*) may result in some differences in the respective immune priming process and MOA. No *in vitro* or animal studies were performed to compare the direct or indirect effects of MCNA and BCG on tumor cells, or how the effects of MCNA may be altered by, or dependent on, prior exposure to BCG. Additionally, Studies 301 or 303 did not enroll any BCG-naïve subjects. Thus, it is unclear if prior treatment with BCG was necessary to prime the responses to MCNA treatment observed in these trials. In addition, it is unclear at what time point in the clinical course, i.e., how many prior BCG treatments these patients need to receive prior to receiving MCNA, which may have an MOA similar to BCG.

Discussion Topic # 5a: *Please discuss the possible explanations for the observed responses from treatment with MCNA, an agent which may have an MOA similar to BCG, in subjects whose disease did not appear to respond to further BCG therapy.*

Discussion Topic # 5b: *Please discuss whether prior treatment with BCG is required to prime the MCNA response.*

6. Overall Benefit-Risk Profile

The proposed indication for MCNA is for "treatment of NMIBC at high risk of recurrence or progression in adult patients who failed prior Bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing." Please consider the background information and evidence of benefit and risk provided in the briefing documents, as well as the presentations and discussions during this meeting.

Discussion Topic # 6: *Please discuss whether MCNA has an overall favorable benefit-risk profile for the treatment of non-muscle invasive bladder cancer at high risk of recurrence or*

progression in adult patients who failed prior BCG immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing.

Voting Question: *Does MCNA have an overall favorable benefit-risk profile for the treatment of non-muscle invasive bladder cancer at high risk of recurrence or progression in adult patients who failed prior BCG immunotherapy, e.g., in patients who are BCG-refractory or BCG-relapsing?*